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EXAMINER
AFREMOVA, VERA

ART UNIT	PAPER NUMBER
1651	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/646,899	Applicant(s) Maeda et al.
	Examiner Vera Afremova	Art Unit 1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 24, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above, claim(s) *7 and 12-19* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6 and 8-11* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to comply with SEQ requirements*

DETAILED ACTION

Claims 1-19 are pending.

Restriction/Election

Applicants' election with traverse of the Group I invention (claims 1-4 and 8-11), drawn to a method for differentiating osteoclast precursor cells, in the Paper No. 6 filed 6/24/2002 is acknowledged. The traversal is on the ground(s) that the claims of all groups are presented in dependent form and, thus, they are linked by a special technical feature. This is not found persuasive for the reasons as explained in the prior office action with regard to different categories of inventions. Moreover, the special technical feature (cellular product such as osteoclast precursor cell and/or osteoclast cell) is known the prior art, for example: see the cited WO 96/07733 at page 29, lines 32-34. Thus, the inventive link is broken. Therefore, the requirement is still deemed proper and is therefore made FINAL. Claims 7 and 12-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions. The Group II claims 5 and 6, drawn to a method for isolating osteoclast precursor cells, have been rejoined with the Group I claims, drawn to a method for differentiating osteoclast precursor cells.

Claims 1-6 and 8-11 are under examination in the instant office action.

Specification

This application contains sequence disclosures (see page 5, lines 21 and attachment 1/1) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in

37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice to Comply With Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Failure to comply with these requirements will result in abandonment of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Rejections - 35 USC § 112

Claims 1-6 and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite and incomplete because the claimed method is intended for differentiating osteoclast precursor cells but it neither results in the possession of differentiated osteoclast cell nor it is certain what is a differentiated osteoclast precursor cell as claimed, if any.

Claims 2 and 3 are rendered indefinite by the phrase "uses a culture medium" because it is uncertain as claimed what active steps are intended by this phrase and what types of cells are intended for a culture medium containing cytokines of claim 2 or supernatant of claim 3.

Claim 2 is indefinite with regard to eotaxin-3 because it is not particularly clear as claimed and as disclosed whether this compound is a prior art product (commercially available product) or whether it is the applicants' particular products (see specification page 5, last par.).

The rejections above are also applied to claims 8-11.

Claim 5 is indefinite and incomplete because the claimed method is intended for isolating osteoclast precursor cells but it neither results in the possession of osteoclast precursor cells nor it is certain what is a osteoclast precursor cell as claimed, if any. This claim is also rendered indefinite by the phrase "peripheral blood or joint fluid in the absence of cytokine" because it is uncertain whether cytokines were removed from blood or joint fluid and what components were cultured as intended.

Claim 6 is rendered indefinite by the phrase "culturing them" because it is uncertain what is cultured. Is it whole blood or joint fluid sample? What cells are intended by the phrase "them"? Claim 6 is also rendered indefinite by the phrase "culturing ... to perish cells except osteoclast precursor cells" because it is uncertain what "cells" perish and how it is determined.

Claim 8 is indefinite and incomplete because it is uncertain what cells are obtained in the method of claim 5 and whether the "accessory cells" have been removed from blood and joint fluid.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by US 5,830,682 [A].

Claim is directed to a method for differentiating osteoclast precursor cells wherein the method comprises step of culturing osteoclast precursor cells in the absence of accessory cells.

US 5,830,682 [A] teaches a method for differentiating osteoclast precursor cells wherein the method comprises culturing non-adherent bone marrow derived osteoclast precursor cells at 37°C in 5% CO2 in the absence of accessory cells (see example 1). The disclosed method does not comprise the use of any additional feeder cells or stromal cells and, thus, the non-adherent bone marrow derived osteoclast precursor cells are cultured in the absence of accessory cells as required by the presently claimed method.

Claims 1, 5, 6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Purton et al. [U].

Claims are directed to a method for isolating osteoclast precursor cells wherein the method comprises culturing peripheral blood derived cells in essential medium for mammalian cells in the absence of cytokines for 1-3 weeks. Some claims are/are further drawn to differentiating osteoclast precursor cells by culturing osteoclast precursor cells in the absence of accessory cells.

Purton et al. [U] disclose a method for isolating osteoclast precursor cells wherein the method comprises culturing peripheral blood derived mononuclear cells at standard culture conditions in the essential medium for mammalian cells such as MEM in the absence of cytokines for up to 21 days or for 1-3 weeks. The disclosed method does not comprise the use of any additional feeder cells or stromal cells and, thus, the peripheral blood derived mononuclear cells comprising osteoclast precursor cells are cultured in the absence of accessory cells as required by the presently claimed method.

Claims 1, 2, 5, 6, 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Matayoshi et al. [V].

Claims are directed to a method for isolating osteoclast precursor cells wherein the method comprises culturing peripheral blood derived cells in the essential medium for mammalian cells in the absence of cytokine for 1-3 weeks. Some claims are/are further drawn to differentiating osteoclast precursor cells by culturing osteoclast precursor cells in the absence of accessory cells. Some claims are further drawn to the use of cytokines such as IL-3 and/or GM-CSF.

Matayoshi et al. [V] disclose a method for isolating and differentiating osteoclast precursor cells wherein the method comprises culturing peripheral blood derived hematopoietic precursor CD34+ cells in the essential medium for mammalian cells such as MEM in the absence of cytokines and in the absence of accessory cells for up to 4-6 weeks at standard culture

conditions *in vitro*. The cited reference also teaches the use of cytokines such as IL-3 and/or GM-CSF for differentiating osteoclast precursor cells by culturing osteoclast precursor cells in the absence of accessory cells *in vitro* (Fig. 6). The cited reference is considered to anticipate the claimed invention because it teaches the identical method for isolating and differentiating osteoclast precursors cells in the absence of accessory cells and method for differentiating osteoclast precursors by using various cytokines including IL-3 and/or GM-CSF. Both the presently claimed method and the cited method encompass the use of identical source or identical starting material for obtaining osteoclast precursor cells such as the use of peripheral blood in the claimed method and the use of the *in vivo* mobilized peripheral blood hematopoietic CD34+ precursor of osteoclast cells in the cited method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 and 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matayoshi et al. [V] taken with Purton et al. [U], US 5,830,682 [A], US 5,879,940 [B] and Lorenzo et al. [W].

Claims 1, 2, 5, 6, 8 and 9 are explained above. Claims 3, 4, 10 and 11 are further drawn to the use of a supernatant of phytohemagglutin-stimulated human blood peripheral mononuclear cells in the culture medium for osteoclast precursor cells.

The cited references Matayoshi et al. [V], Purton et al. [U] and US 5,830,682 [A] are relied upon as explained above for the disclosure of the method for culturing hematopoietic precursor of osteoclast cells including peripheral blood derived cells {Matayoshi et al. [V], Purton et al. [U]} in the absence of accessory cells {Matayoshi et al. [V], Purton et al. [U], US 5,830,682 [A]} at standard culture conditions such as 37°C in 5% CO2 {US 5,830,682 [A]}. The cited references are missing particular disclosure related to the use of a supernatant of phytohemagglutin-stimulated human blood peripheral mononuclear cells in the culture medium for osteoclast precursor cells.

However, it is known in the prior art to use a supernatant (or conditioned medium) of phytohemagglutin-stimulated human blood peripheral mononuclear cells in the culture medium for hematopoietic precursor cells (for example: see US 5,879,940 at col. 11, lines 20-26) wherein hematopoietic precursor cells are derived from various sources including peripheral blood, bone marrow and other sources (for example: see US 5,879,940 at col. 4, lines 54-60). Further, Lorenzo et al. [W] (see page 1164, col. 1, lines 3-7) teaches that a supernatant of phytohemagglutin-stimulated human blood peripheral mononuclear cells contains osteoclast activating factor which stimulates differentiation of osteoclast precursor cells or development of bone resorpting activity which is a major feature of mature osteoclast cells.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use a supernatant of phytohemagglutin-stimulated human blood peripheral mononuclear cells in the culture medium for osteoclast precursor cells with a reasonable expectation of success in obtaining osteoclast precursor cells and/or osteoclast cells because it has been known in the prior art to use a supernatant of phytohemagglutin-stimulated human blood peripheral mononuclear cells in the culture medium for hematopoietic osteoclast precursor cells. One of skill in the art would have been motivated to use a supernatant of phytohemagglutin-stimulated human blood peripheral mononuclear cells in the culture medium for osteoclast precursor cells for the benefit of obtaining osteoclast cells and/or their precursors and for the benefit of studying normal and abnormal skeletal metabolism including bone-resorpting activity, a major function of osteoclasts. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claims 1-6 and 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matayoshi et al. [V] taken with Purton et al. [U], US 5,830,682 [A], US 5,879,940 [B], Lorenzo et al. [W] and further in view of Kitaura et al. [X], Forsman et al. [U-1], Onoe et al. [W-1] and Dahl et al. [V-1].

Claims 1-6 and 8-11 as explained above. Some claims are drawn to the use of additional cytokines such as eotaxins or il-7 in the method for differentiating osteoclast precursors. Some claims are drawn to the use of additional source of osteoclast precursor cells such as joint fluid.

The cited references Matayoshi et al. [V], Purton et al. [U], US 5,830,682 [A], US 5,879,940 [B] and Lorenzo et al. [W] are relied upon as explained above for the disclosure of methods for isolating and differentiating cells of hematopoietic lineage including osteoclasts.

The reference by Kitaura et al. [X] and Forsman et al. [U-1] (see abstracts)are relied upon to demonstrate that eotaxins have been used for culturing hematopoietic precursor cells and that eotaxins have been taught as factors responsible for cellular activity of cells of hematopoietic lineage. And the reference by Onoe et al. [W-1] (abstract) is relied upon for the teaching that various cytokines including il-7 regulate bone-resorpting activity of osteoclasts.

Further, Dahl et al. [V-1] is relied upon for the teaching that synovial tissue or joint fluid derived from patient with rheumatoid arthritis contains substantial amounts of cells of hematopoietic lineage including cells of macrophage nature.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use synovial tissue or joint fluid derived from patient with rheumatoid arthritis as the source of cells of hematopoietic lineage including cells of macrophage nature as taught by Dahl et al. [V-1] with a reasonable expectation of success in obtaining cells of macrophage nature including osteoclast precursor cells because cells of macrophage nature and/or osteoclast precursor derive from the same pluripotent precursor cells as taught by

Matayoshi et al. [V] (see page 10785, col.1, lines 1-3). One of skill in the art would have been motivated to use eotaxins in the culture medium for hematopoietic cells including macrophage and/or osteoclast precursor cells for the benefit of regulating cellular activity of these cells as taught by Kitaura et al. [X] and Forsman et al. [U-1]. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova,

Art Unit 1651

September 3, 2002.

IRENE MARX

PRIMARY EXAMINER